

In the Specification:

Please amend the specification as shown:

Please insert the Sequence Listing paper copy, attached herewith, into the application.

Please delete paragraph [0048] and replace it with the following paragraph:

[0048] Figure 1 schematically illustrates the location of the enhancer II region on the Hepatitis B virus just upstream of the core promoter. This region (see also figure 6) has been shown to be involved in viral replication. **Figure 1 discloses SEQ ID NO: 40.**

Please delete paragraph [0052] and replace it with the following paragraph:

[0052] Figure 5 illustrates that distinct segregation between high and low viraemic HBV individuals is correlated to changes at nucleotide position 1752. Data of the corresponding DNA sequences from nucleotide 1720 to 1769 to the HBV DNA titer levels of patients are illustrated. A total of 60 patients were collated and DNA was isolated from sera and amplified with two rounds of PCR. PCR products were purified and sequenced directly to confirm the identity of the products. Results of the sequences were aligned and compared. **Figure 5 discloses SEQ ID NOS: 41-63, 41 and 64-99, respectively, in order of appearance.**

Please delete paragraph [0053] and replace it with the following paragraph:

[0053] Figure 6 renders the sequence of the enhancer II region of HBV (**SEQ ID NO: 100**). The position of the point mutation identified as being related to a change in levels of serum HBV DNA in infected donors is marked. The minimum sequence for enhancer activity has been previously defined at nucleotide 1687-1805 of the HBV genome as published at NCBI accession No NC_003977 (Yee JK, *Science* 246, 1989, 658-661; Wang Y et al., *J Virol.* 64 (8), 1990,

3977–3981; Yuh CH, Ting LP, *J Virol.* 64 (9), 1990, 4281–4287). Variants of this enhancer have previously been linked with lower replication rates of HBV *in vivo* (Uchida T et al., *Microbiol Immunol* 38, 1994, 281–285). Some of the early publications do not refer to the sequence of the said NCBI accession No and thus deviate slightly in nucleotide counting.

Please delete paragraph [0056] and replace it with the following paragraph:

[0056] Figure 9 depicts the amino acid sequences and the corresponding encoding cDNA sequences of the known variants of hnRNP K (Genebank Accession numbers for variants 1, 2 and 3 are NM_002140, NM_031262, and NM_031263 respectively). Variant 3 and variant 1 differ in their 5'untranslated regions (UTRs) and not in their encoding regions, hence only one example is given. Variant 2 contains a deletion of 60 bases at the end of the coding region in comparison to the other two known variants, resulting in a frame shift. Consequently its extreme C-terminus differs from the other two variants. So far no comparative studies have been published on functional differences between the two variants. **Figure 9 discloses SEQ ID NO: 101 coding SEQ ID NO: 102 and SEQ ID NO: 103 coding SEQ ID NO: 104.**

Please delete paragraph [0066] and replace it with the following paragraph:

[0066] Figure 18 shows an in-vitro measurement of the complex formation between fragments of HBV DNA (**SEQ ID NO: 106**) and a hnRNP K protein in an Electrophoretic Mobility Shift Assay (EMSA). 28-mer oligonucleotide probes were designed to contain either the 1752A or 1752G nucleotide with control probes taken from the adjacent upstream sequence. EMSA was performed using HepG2 nuclear extracts with the four respective probes. Probe 1 (SEQ ID NO: 12): Lanes 1 to 4; Probe 2 (SEQ ID NO: 13, A¹⁷⁵²): Lanes 5 to 8; Probe 3 (SEQ ID NO: 14 **105**): Lanes 9 to 12; Probe 4 (SEQ ID NO: 15, G¹⁷⁵²): Lanes 13 to 16. Each set of probes contains increasing concentrations (0.0 μg, 0.05 μg, 0.10 μg and 0.15μg) of non-specific

competitor DNA of [poly-(dI)-poly-(dC)] respectively. This competitor DNA is included to minimize the binding of nonspecific proteins to the labeled probes. DNA-protein complexes migrate at a different speed than free DNA molecules. Binding of hnRNP K is therefore indicated by a signal of different mobility from the HBV DNA probe. Verification of the presence of hnRNP K as the second component in the complex can subsequently be performed by an analysis as shown in figure 19. hnRNP K was detected using the 1752A probe (Probe 2, lanes 5 to 8) along with a weaker band of similar size using the 1752G probe (Probe 4, lanes 13 to 16). Densitometric analysis of the bands indicated that the protein detected by Probe 2 was about 300 % higher than that detected by Probe 4, suggesting that the 1752A probe has a higher binding affinity for hnRNP K.

Please delete paragraph [0067] and replace it with the following paragraph:

[0067] Figure 19 shows the identification of the complex formation between HBV and a cellular protein. 40 µg of nuclear protein extracts obtained from HepG2 cells were allowed to bind onto 5 mg DynabeadsR M-280 streptavidin-biotin-oligonucleotides in the presence of 2:1 (w/w) ratio of non-specific competitor DNA poly (dI-dC). Unbound proteins were washed out, bound proteins were eluted and loaded to 18 cm, pH 3 to 10 nonlinear Immobiline drystrips. Rehydration was carried out at constant voltage (50 V) overnight. First dimensional isoelectric focusing was followed by second dimensional vertical separation on SDS-PAGE (10%). The estimated molecular weight of the specific protein spots detected by silver staining (arrow) is indicated.e. It also revealed that specific protein spots appeared at a molecular weight of approximately 56 kDa. **Probes 1 and 2 are disclosed as SEQ ID NOS: 12 and 13, respectively.**

Please delete paragraph [0068] and replace it with the following paragraph:

[0068] **Figure 20** shows the identification of the cellular protein. Specific protein spots were cored out and destained according to manufacturer's instructions, following which the gel plug was alkylated with iodoacetamide and digested with trypsin. A tryptic mass map was obtained by means of Matrix-Assisted Laser Desorption/Ionization mass spectroscopy (MALDI). Sequence query of peptide fragments was carried out in Proteomic Research Services, Inc by using LC/MS/MS analysis (<http://www.proteomicresearchservices.com/>). Results of the 21 obtained and sequenced peptides are illustrated. Sequence alignments of the 56 kDa protein revealed high homology scores to hnRNP K proteins. Furthermore the molecular mass of the analysed protein matched that of hnRNP K proteins. **Figure 20 discloses SEQ ID NOS: 107-127, respectively, in order of appearance.**

Please delete paragraph [0069] and replace it with the following paragraph:

[0069] **Figure 21** depicts the amino acid sequence of the known hnRNPK variants (**SEQ ID NOS: 128 and 129, respectively, in order of appearance**) (see also figure 9) and the respective regions covered by tryptic peptides (boxes) assigned by MALDI peptide mass mapping (**SEQ ID NOS: 130-136, respectively, in order of appearance**).

Please delete paragraph [0086] and replace it with the following paragraph:

[0086] Cells were transfected with the HBV 1752A replicative construct as described in Example 1. 4 μ g of plasmid DNA was transfected using Lipofectamine 2000. After incubation for 6 h at 37 °C a panel of different anti-EGFR immunoglobulins (see figure 15) was added. **Ab1** (AnaSpec, San Jose, CA, USA Cat # 29615) is a rabbit anti-EGFR (phosphospecific) polyclonal immunoglobulin raised against a synthetic peptide corresponding to the tyrosine phosphorylated site of 1016 of human EGFR (this sequence is identical in mouse and rat origins). The immunoglobulin is supplied as an epitope affinity purified rabbit IgG, 100 μ g in 200 μ l

phosphate buffered saline (pH7.4) containing 0.02% Proclin300. 0.22 μ g/ μ l was used for each cell assay as shown in Fig. 15. **Ab 2** (Research Diagnostics, Flanders NJ, USA, Cat # RDI-EGFRabS) is a sheep anti-EGFR immunoglobulin raised against recombinant human EGFR (partial cytoplasmic domain of EGFR inclusive of region relevant to exon 15-18). The immunoglobulin is supplied as 200 μ g IgG in 200 μ l Tris-HCl (pH 7.4) with 0.05% sodium azide. 0.43 μ g/ μ l was used for each cell assay. **Ab 3** (Research Diagnostics, Cat # RDI-EGFRCabrX) is a rabbit immunoglobulin raised against a synthetic peptide from amino acid position 1168 to 1181 (NH₂-C-S-L-D-N-P-D-Y-Q-Q-D-F-F-P-K-E-COOH) (SEQ ID NO: 39), mapping to a region near the carboxy-terminus which is identical in human, mouse and rat EGFR. The amino terminal cysteine was synthesized to facilitate carrier coupling. Recognition of EGFR is independent of the phosphorylation status at tyrosine 1173. No reaction was observed against erbB-2, erbB-3 or erbB-4. The immunoglobulin is supplied as 250 μ l sterile filtered neat sera with approximately 85 mg/ml protein concentration. 46 μ g/ μ l was used for each cell assay. **Ab 4** (Sigma, St. Louis, MO, USA, Cat # A204) is a sheep immunoglobulin raised against a 20 amino acid fusion protein of the human EGFR as the immunogen. This sequence is proximal to the phosphorylation region (near the N-terminal sequence). The immunoglobulin recognizes the internal domain of the receptor molecule and will block the phosphorylation but not the binding of EGF. The immunoglobulin is supplied as a 1.3 mg/ml sterile-filtered solution in 0.15 M phosphate buffered saline (pH 7.5). 0.1 μ g/ μ l was used for each cell assay. Fresh aliquotes of immunoglobulins were added at 24 h post-transfection to enhance blocking effects. Cells were further incubated and 48 h post-transfection harvested followed by genomic DNA extraction with the DNeasy Kit (Qiagen). HBV viral titer loads were measured by real-time PCR using the RealArt HBV LC PCR Kit (Artus GmbH) according to manufacturer's instructions in the LightCycler Instrument (Roche Diagnostics GmbH).